03-13-06

AF/EJW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Basi, Nirmal Singh
Avi ASHKENAZI, *et al.*	)	Art Unit: 1646
Application Serial No. 09/909,088	)	Confirmation No: 1981
Filed: July 18, 2001	)	Attorney's Docket No. 39780-1618 P2C79
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING SAME**	)	**Customer No. 35489**

EXPRESS MAIL LABEL NO.: EL 765 981 828 US
DATE MAILED: MARCH 10, 2006

ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES
APPELLANTS' BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents -
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On August 11, 2005, the Examiner made a final rejection to pending Claims 39-47 and 49-51. A Notice of Appeal was filed on October 28, 2005.

Appellants hereby appeal to the Board of Patent Appeals and Interferences from the last decision of the Examiner. This response is timely filed requesting a three-month extension of time with fees.

The following constitutes Appellants' Brief on Appeal.

1. REAL PARTY IN INTEREST

The real party in interest is Genentech, Inc., South San Francisco, California, by an assignment of the parent application, U.S. Patent Application Serial No. 09/665,350 recorded July 9, 201, at Reel 011964 and Frame 0181.

2. RELATED APPEALS AND INTERFERENCES

The claims pending in the current application are directed to a polypeptide referred to herein as "PRO335." There exists two related patent applications: 1) U.S. Patent Application Serial No. 09/903, 520, filed July 11, 2001 (containing claims directed to PRO335 polypeptides), and 2) U.S. Patent Application Serial No. 09/904,786, filed July 12, 2001 (containing claims directed to PRO335 antibodies). These applications are also under final rejection from the same Examiner and based upon the same type of outstanding rejections, and an appeal of these final rejections is being pursued independently and concurrently herewith.

3. STATUS OF CLAIMS

Claims 39-47, 49-52 and 55-58 stand rejected in this application and Appellants appeal the rejection of these claims. Claims 48 and 53-54 were canceled.

A copy of the rejected claims involved in the present Appeal is provided as Appendix A.

4. STATUS OF AMENDMENTS

There were no amendments submitted after final rejection. All previous amendments have been entered.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The invention claimed in the present application is related to isolated polynucleotides comprising a nucleic acid sequence encoding the polypeptide of SEQ ID NO:290 referred to in the present application as "PRO335," a nucleic acid sequence encoding the polypeptide of SEQ ID NO:290, or a nucleic acid sequence encoding the polypeptide of SEQ ID NO:290 lacking its associated signal peptide; or the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:289; or a nucleic acid sequence of the full-length coding sequence of the cDNA deposited

under ATCC accession number 209927 (Claims 44-47 and 49). The invention is further directed to nucleic acids having at least 80-99% sequence identity to nucleic acids encoding polypeptides of SEQ ID NO:290; or the nucleic acid sequence encoding the polypeptide of SEQ ID NO:290 lacking its associated signal peptide; or the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:289; or the nucleic acid sequence of the cDNA deposited under ATCC accession number 209927, wherein the polypeptide encoded by said nucleic acid is an immunostimulant (Claims 39-43).

The invention is further directed to vectors comprising these nucleic acids and host cells comprising such vectors (page 117 to page 123). PRO nucleic acid variants having at least about 80% nucleic acid sequence identity with a nucleic acid encoding for a full length PRO polypeptide sequence or a PRO polypeptide sequence lacking the signal peptide are described in the specification at page 55, line 2 to page 57, line 10, and for example, at page 69, line 25 to page 72, line 8.

The cDNA nucleic acid encoding PRO335 is described in the specification at, for example, page 184, line 21 to page 185, line 32 (Example 43), in Figure 101 and in SEQ ID NO:289. Page 63, lines 34-37 of the specification provides the description for Figures 101 and 102. The full-length PRO335 polypeptide having the amino acid sequence of SEQ ID NO:290 is described in the specification at, for example, page 50-51, lines 1-22, in Figure 102 and in SEQ ID NO:290.

Recombinant expression, characteristics and effects of the PRO335 polypeptides were disclosed in the specification, including in Examples 43, 54, 56, 74, and 77. The PRO335 polypeptides encoded by the claimed nucleic acids were shown to induce proliferation of stimulated T-lymphocytes in a mixed lymphocyte reaction as compared to controls (Example 74). PRO335 is also described as a polypeptide having homology to proteins of the leucine rich repeat superfamily, and particularly, are related to LIG-1 (page 30, line 11, to page 31, line 18, and page 110, lines 26-36). Example 74 (page 208) shows that PRO335 tested positive in the mixed lymphocyte reaction (MLR) assay, demonstrating that PRO335 is active as a stimulator of the proliferation of stimulated T-lymphocytes, and therefore would have utility in the treatment of

conditions where the enhancement of an immune response would be beneficial. In addition, Example 77 shows the ability of PRO335 to stimulate an immune response and induce inflammation at the site of injection in the skin vascular permeability assay, using the hairless guinea pig injected with the Evans blue dye as a model system.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Whether the data generated in the MLR assay (Example 74) satisfies the enablement requirement set forth in 35 U.S.C. §112, first paragraph, for the invention claimed in Claims 39-47, 49-52 and 55-58.

II. Whether Claim 52 is anticipated under 35 U.S.C. §102(b) by the disclosure of the Amersham Life Sciences Catalog (1996).

7. ARGUMENT

Summary of the Arguments:

Issue I: Enablement

The Examiner asserts that "there is no guidance as to how PRO335 could be used to boost the response to any antigen." Since the 'how to use' prong of the enablement requirement under 35 U.S.C. §112, first paragraph incorporates, as a matter of law, a requirement that the specification disclose a practical utility for the claimed invention, and the utility requirements under 35 U.S.C. §101 are discussed.

Appellants submit that patentable utility for the PRO335 polypeptide is based upon data derived from the mixed leukocyte reaction (MLR) assay. The MLR assay is a well-established and accepted assay in the art for evaluating test compounds for their ability to stimulate T-lymphocyte proliferation *in vitro*. Example 74 of the instant specification shows that PRO335 tested positive in the mixed lymphocyte reaction (MLR) assay, demonstrating that PRO335 is active as a stimulator of the proliferation of stimulated T-lymphocytes, and therefore has utility in the treatment of conditions where the enhancement of an immune response would be beneficial, like to treat tumor progression/ regression in cancer.

Appellants also note that the claimed variants recite those nucleic acids having at least

80% nucleic acid sequence identity to the nucleic acid encoding the polypeptide sequence of SEQ ID NO:290 or the nucleic acid sequence of SEQ ID NO:289 and further, which recite the functional recitation "wherein said polypeptide is an immunostimulant." Thus, each claimed variant shares an immunostimulant property besides having sequence identity to the nucleic acid sequence encoding the PRO335 polypeptide. The specification provides ample guidance to the skilled artisan to identify variant nucleic acids with sequence identity and includes a detailed protocol of the MLR assay.

Moreover, there was vast knowledge available as a whole in the filed of immunology (immunostimulants), at and around the effective date of filing of the instant application (September 17, 1998), which sufficiently provided a nexus between the use of immunostimulants in the treatment of a variety of disease conditions, like tumor progression/ regression in cancer. Appellants have further submitted with their Response of August 30, 2004, a Declaration by Dr. Sherman Fong, an expert in the field of Immunology and inventor in this application, which explains the ability of immunostimulants to stimulate immune response and their role in treating important clinical conditions like tumor progression/regression, etc. For example, the Declaration discussed exemplary immune stimulants like IL-12 that show activity in a mixed lymphocyte reaction assay, and are useful to treat diseases like melanoma due to its ability to stimulate the immune response. Dr. Fong's Declaration states that "a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant." The specification discloses that PRO335 has an activity of at least 180% of the control (see Example 74 of the instant specification).

Therefore, Appellants submit that they have provided patentable utility for the claimed PRO335 molecule as an immunostimulant and in view of the teachings of the instant specification and the knowledge in the field of immunology, one of ordinary skill in the art would understand exactly how to use the recited nucleic acid variants to treat disease without any undue experimentation.

These arguments are all discussed in further detail below under the appropriate headings.

Issue II: Anticipation

The cited Amersham Life Sciences Catalog (1996) only discloses radioactive and dye-labeled nucleotides useful in various assays such as labeling reactions, DNA sequencing, protein kinase assays, etc. Therefore, these nucleotides clearly do not anticipate the instantly claimed "isolated **nucleic acid molecule consisting of a fragment of the nucleic acid sequence of SEQ ID NO: 289**, or a complement thereof, that specifically hybridizes under stringent conditions" of Claim 52. The stringent hybridization conditions are a claimed element of Claim 52. Further, Appellants submit that the cited nucleotides of the Amersham catalog would not specifically hybridize to the fragment of SEQ ID NO: 289 under the stringent hybridization conditions recited.

These arguments are all discussed in further detail below under the appropriate headings.

Detailed Arguments:

ISSUE I: The Data Generated in the MLR Assay Satisfies the Utility/ Enablement Requirement of 35 U.S.C. §§101/112, First Paragraph for Claims 39-47, 49-52 and 55-58

Since the 'how to use' prong of the enablement requirement under 35 U.S.C. §112, first paragraph incorporates, as a matter of law, a requirement that the specification disclose a practical utility for the claimed invention, and the utility requirements under 35 U.S.C. §101 are discussed below. Appellants submit that the results of the MLR assay in the instant specification (and in the priority U.S. Provisional Patent Application Serial No. 60/100,858) provides at least one credible, substantial and specific asserted utility for the claimed nucleic acids encoding PRO335 polypeptides under 35 U.S.C. §101/§112, first paragraph.

A. Legal Standard for Utility

According to 35 U.S.C. §101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added).

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001), an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In. explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a "substantial" utility." (M.P.E.P. §2107.01, Emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record ... that is probative of the applicant's assertions." (M.P.E.P. §2107 II(B)(1)(ii)). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion

(Revised Interim Utility Guidelines Training Materials, 1999).

The case law has clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[1] The PTO has the initial burden to prove that applicant's claims of usefulness are not believable on their face.[2] In general, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[3, 4]

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines"),[5] which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard

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[1] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[2] *Ibid.*

[3] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[4] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[5] 66 Fed. Reg. 1092 (2001).

to defining a 'substantial' utility.'"[6] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[7] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Appellants note that the phrase cited above "useful for any practical purpose" merely requires that an invention be useful, and does not require that it be *better* than other competing subject matter: "The Federal Circuit stated that a finding that "an invention that is an 'improvement' is not a prerequisite to patentability" since it "is possible for an invention to be less effective than existing devices but nevertheless meet the statutory criteria for patentability." (*Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.)*[8]

In interpreting the utility requirement, in *Brenner v. Manson,*[9] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, *i.e.,* a utility "where specific benefit exists in currently available form."[10] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[11]

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[6] M.P.E.P. §2107.01.

[7] M.P.E.P. §2107 II(B)(1).

[8] *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 1 USPQ2d 1196 (Fed. Cir. 1986).

[9] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[10] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[11] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

Later, in *Nelson v. Bowler,*[12] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The Court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[13]

Moreover, in *Cross v. Iizuka,*[14] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, *i.e.,* there is a reasonable correlation there between."[15] The Court perceived, perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility."[16]

Furthermore, M.P.E.P. §2107.03 (III) states that:

> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process.

Thus, the legal standard accepts that *in vitro* or animal model data is acceptable utility as long as the data is "reasonably correlated" to the pharmacological utility described.

Compliance with 35 U.S.C. §101 is a question of fact.[17] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the

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[12] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[13] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[14] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[15] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[16] *Id.*

[17] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) *cert. denied,* 469 US 835 (1984).

totality of the evidence under consideration.[18] Accordingly, Appellants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. With respect to asserted therapeutic utilities based upon *in vitro* data, an applicant "does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty."[19] The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

B. Proper Application of the Legal Standard

Appellants submit that the results of the mixed lymphocyte reaction (MLR) assay described in Example 74 of the instant specification (and in the priority U.S. Provisional Patent Application Serial No. 60/100,858) provides at least one credible, substantial and specific asserted utility for the claimed nucleic acids encoding PRO335 polypeptides under 35 U.S.C. §§101/112, first paragraph, based on the positive results for the PRO335 polypeptide in the MLR assay described at page 208 of the specification. Example 74 demonstrates that PRO335 is active as a stimulator of the proliferation of stimulated T-lymphocytes.

The MLR was a well-established assay at the priority date of the present application (September 17, 1998) for evaluating test compounds, such as the PRO335 polypeptide, for their

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[18] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[19] M.P.E.P. §2107.03.

ability to stimulate T-lymphocyte proliferation *in vitro*, and consequently, for assessing the immune response of an individual. The MLR assay is well-described in standard textbooks, including, for example, *Current Protocols in Immunology*, unit 3.12; edited by J E Coligan, A M Kruisbeek, D H Marglies, E M Shevach, W Strober, National Institutes of Health, Published by John Wiley & Sons, Inc. (1991) which is referenced in Example 74, the entire content of which is expressly incorporated by reference into the disclosure of the present application (see page 147, line 16-17). In brief, in this method, an immune response results upon mixing T-cells from antigenically distinct individuals under cell culture conditions. An MLR reaction can be monitored quantitatively by, for example, following the incorporation of tritiated thymidine during DNA synthesis, or by observing blast formation, or by other methods well known in the art.

According to the specification, positive increases over control in this assay are considered to be positive results, with increases of greater than or equal to 180% being preferred. However, any value greater than control indicates a stimulatory effect for the test protein. PRO335 (SEQ ID NO: 290) tested positive in this assay, using the described criteria. Example 74 further explains that compounds which stimulate proliferation of lymphocytes in this assay "are useful therapeutically where enhancement of an immune response is beneficial." Accordingly, PRO335 has utility in the treatment of conditions where the stimulation of lymphocyte proliferation would be desirable, like to treat tumor progression/ regression in cancer.

In further support of utility based upon the MLR assay, Appellants have submitted (with their Response filed August 30, 2004) the Declaration of Sherman Fong, Ph.D. Dr. Fong is an inventor of the above-identified patent application, and an experienced scientist familiar with the MLR assay, which was used by him and others under his supervision, to test the immune stimulatory or immune inhibitory activity of novel polypeptides discovered in Genentech's Secreted Protein Discovery Initiative project, including PRO335. The Fong Declaration explains how the MLR reaction was performed in the instant application using peripheral blood mononuclear cells (PBMCs), which contain responder T-cells, and allogenic, pre-treated (irradiated) PBMCs, which predominantly contained dendritic cells. Dr. Fong proceeds to

explain (paragraph 7 of the Declaration) that dendritic cells are potent antigen-presenting cells that are able to "prime native T cells *in vivo*." Once activated by dendritic cells, the T-cells are capable of interacting with other antigen-presenting cells (B cells and macrophages) to produce additional immune responses from these cells.

As Dr. Fong states, "the MLR assay of the present application is designed to measure the ability of a test substance to "drive" the dendritic cells to induce the proliferation of T-cells that are activated, or co-stimulated in the MLR, and thus identifies immune stimulants that can boost the immune system to respond to a particular antigen that may not have been immunologically active previously" (Paragraph 8 of the Fong Declaration). Dr. Fong also emphasizes that, immunostimulants are important and highly desirable in the treatment of cancer and in enhancing the effectiveness of previously identified treatments for cancer. Supportive evidence for this teaching comes from the art such as Steinman *et al.* (submitted as Exhibit B with the Amendment filed August 30, 2004) who state that "...**medicine needs therapies that enhance immunity or resistance to infections and tumors**" (page 1, column 1, line 7; emphasis added).

In paragraph 9 of his Declaration, Dr. Fong provides examples of important clinical applications for immune stimulants which have been shown to stimulate T-cell proliferation in the MLR assay. As Dr. Fong explains,

> "IL-12 is a known immune stimulant, which has been shown to stimulate T-cell proliferation in the MLR assay [Gubler *et al.* PNAS 88, 4143 (1991) (Exhibit C)]. IL-12 was first identified in just such an MLR. In a recent cancer vaccine trial, researchers from the University of Chicago and Genetics Institute (Cambridge, MA) have demonstrated the efficacy of the approach, relying on the immune stimulatory activity of IL-12, for the treatment of melanoma. [Peterson *et al.* Journal of Clinical Oncology 21 (12). 2342-48 (2003) (Exhibit D)] They extracted circulating white blood cells carrying one or more markers of melanoma cells, isolated the antigen, and returned them to the patients. Normally patients would not have an immune response to his or her own human antigens. The patients were then treated with different doses of IL-12, an immune stimulant capable of inducing the proliferation of T cells that have been co-stimulated by dendritic cells. Due to the immune stimulatory effect of IL-12, the treatment provided superior results in comparison to earlier work, where patients' own dendritic cells were prepared from peripheral blood mononuclear cells (PBMCs), treated with antigens, then cultured *in vitro* and returned to the patient to stimulate

anti-cancer response. [Thurner *et al.* J. Exp. Med. 190 (11), 1669-78 (1999) (Exhibit E)]."

Therefore, the art, as exemplified by Gubler *et al.* and Thurner *et al.*, in fact supports the Appellants' position that an MLR result is useful for identifying compounds with immunomodulatory activity *in vivo.* Dr. Fong concludes that (paragraph 10):

> It is my considered scientific opinion that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant."

Accordingly, the positive results obtained in this assay clearly establish the immunostimulant utility for the PRO335 polypeptides claimed in the present application, and the specification, in turn, enables one skilled in the art to use the compounds for the asserted purpose.

C. A *prima facie* case of lack of utility has not been established

As a preliminary matter, Appellants submit that, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Appellants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. With respect to asserted therapeutic utilities based upon *in vitro* data, an applicant "does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty" (M.P.E.P. §2107.03.). The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Appellants have asserted that the specification provides sufficient detail to enable one of ordinary skill in the art to conclude that the instant MLR assay is useful to identify compounds having immuno-modulatory activity *in vivo.*

However, the Examiner has asserted on Page 2, last line to page 3, line 6 of the Final Office Action that "no particular antigen is identified in the specification; there is no guidance as to how PRO335 could be used to boost the response to any antigen....Current Protocols in Immunology states on p. 3.12.11 that the MLR only detects dividing cells instead of measuring true effector T-cell function.....it is not clear which T cell function is measured in proliferative assays....the proliferative response should be used solely as a general indicator of T-cell reactivity."

As Appellants have submitted previously in their response filed May 17, 2005, the PRO335 molecule, just like any other immunostimulant (*e.g.*, cytokines), stimulates cellular responses (cellular immunity) rather than a humoral response or any "particular antigen" in the immune system and therefore, the Examiner's rejection based on the premise that "no particular antigen is identified in the specification" is improper. It was well known in the art at the time of filing of the instant application that T-cells are highly important in the body's natural defense mechanisms for fighting infections. For example, viral infections, such as HIV infection, were well known to result of a reduced T-cell count. It was also well known at the time of filing that T-cells could recognize tumor antigens and kill tumors. Therefore, one skilled in the art would reasonably know how to use the PRO335 immunostimulant, for instance, to boost the body's natural defense mechanisms for fighting infections or to recognize tumor antigens and/or to reduce and/or kill tumors. Appellants further submit that the Examiner's general contention in this rejection seems to be concerned with the underlying mechanism of the PRO335 molecule due to a positive result in the MLR assay, and not with the positive result itself. Appellants respectfully submit that this is not a proper basis for a utility rejection. The mechanism of action need not be understood for attaining that utility. In fact, as stated by the Federal Circuit, "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortwright*, 165 F.2d 1353, 1359 (Fed. Cir. 1999). The Federal Circuit has also stated that "[a]n invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is not operable in certain applications is not grounds for

finding lack of utility." *Envirotech Corp. v. Al George, Inc.* 730 F.2d 753,762, 221 USPQ 473,480 (Fed. Cir. 1984)." Thus, Appellants submit that such a concern is misplaced, and cannot properly form the basis of the rejections of the present claims.

The Examiner further contends that "Steinman and Thurner address the utility of dendritic cells but **not** of a stimulatory MLR" (page 3, lines 20-21).

Appellants strongly disagree. The dependence of T-cells upon its interactions with other cells, in particular, with the stimulator cells, have been described in detail in *Current Protocols in Immunology*, unit 3.12; edited by J E Coligan, A M Kruisbeek, D H Marglies, E M Shevach, W Strober, National Institutes of Health, Published by John Wiley & Sons, Inc. (1991), and were also clearly discussed in the Fong Declaration. For instance, Dr. Fong explained in his declaration that "dendritic cells are the most potent antigen-presenting cells that are able to "prime native T-cells *in vivo*" (paragraph 7 of the Declaration). Once activated by dendritic cells, the T-cells are capable of interacting with other antigen-presenting cells (B cells and macrophages) to elicit additional immune responses from these cells. Therefore, by addressing dendritic cells, Steinman and Thurner indeed address stimulatory MLR, as one skilled in the art would readily acknowledge.

The Examiner's misunderstanding of the instant MLR assay is further demonstrated in the Examiner's discussion of "autologous controls" and "statistical results" (see page 3, lines 13-16 of the Final Office Action mailed August 11, 2005). The Examiner has asserted that "Current Protocols in Immunology in fact describes many variables that must be controlled for. In the instant application, no such controls such as for maximum response or for the inherent variability of individual responses are provided. There is no indication of the statistical significance of the results" (emphasis added - see page 3, lines 12-16).

First of all, Appellants submit that the specification clearly indicates that "positive increases over control in this assay are considered to be positive results, with increases of greater than or equal to 180% being preferred" (see Example 74); therefore, contrary to the Examiner's position, controls were discussed in the specification. Further, regarding the Examiner requiring certain types of controls in the assay, again, Appellants submit that the Examiner appears to have

misinterpreted the intent of the controls in the MLR assay throughout this rejection. For instance, the mixing of the stimulator and responder cells in the instant MLR is expected to lead to T-cell proliferation even in the absence of any test protein. The point of the MLR assay is to measure the extent to which the test protein can **enhance** the expected proliferation of the stimulated T-cells. Appellants submit that the controls mentioned by the Examiner are only needed when the purpose of carrying out the MLR assay is to evaluate the properties of the stimulator cells. On the other hand, the purpose of the instant MLR assay, as discussed above, is to characterize test proteins such as PRO335, not stimulator cells. So, the precise extent to which the stimulator cells stimulate the responder cells is not significant; instead, what matters is the degree to which the test protein increases this response. The extent to which the test protein increases the response of the T-cells is measured by comparison to a negative control reaction, which uses either cell culture medium, or a non immunostimulant molecule, CD4-IgG, as a negative control. Because the response in the test reaction is compared to a negative control reaction, and because both reactions use the same stimulator and responder cells at the same time, additional controls to determine the precise properties of these cells are not required.

Further, from the above remarks regarding "statistical data" in the rejection, it is clear that the Examiner is applying a standard that might be appropriate, if the issue at hand were the regulatory approval of PRO335 as an immunostimulant based on the positive result in the MLR assay, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met for PRO335. The FDA, in reviewing an application for a new immunostimulatory agent (drug) will indeed ask for actual numerical data, statistical analysis, and other specific information before the drug is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards for market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to be marketed in the United States. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Indeed, in *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980), the Federal Circuit found that the identification of a pharmacological activity of a

compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to utility for an immunostimulant as well. The identification of an immunostimulantory utility for a compound should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

Accordingly, Appellants respectfully submit that the Examiner's comments fail to support a *prima facie* case of lack of utility.

D. One Skilled in the Art would know how to make and use the variant proteins without undue experimentation based on the teachings in the art and in the specification

The Examiner has rejected the instant claims under 35 U.S.C. §112, first paragraph, allegedly because "without further guidance correlating the observed stimulatory activity to a particular useful property, it would require undue experimentation to use PRO335 ...." (Page 4, lines 3-5 of the Final Office Action mailed August 11, 2005).

Appellants respectfully disagree. The fact remains that the results of the MLR assay were positive, indicating that PRO335 is an immunostimulant. The Examiner 's concern that the results require undue experimentation further, do not negate the positive results of the assay, that is PRO335 is a an immunostimulant molecule, and further, do not negate the assertion of utility for PRO335 polypeptides. As discussed above, one of ordinary skill in the art in possession of these results would, more likely than not, acknowledge that the PRO335 polypeptides are useful as an immunostimulant agents. Moreover, as the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."[20] As discussed above, a considerable amount of experimentation is permissible, if it is merely routine.

Appellants also note that the claimed variants all share the functional recitation that "wherein said polypeptide is an immunostimulant." Example 74 of the present application provides detailed protocols for the MLR assay, including the extensive step-by-step guidance

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[20] M.P.E.P. §2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985).

from Current Protocols in Immunology, which is explicitly incorporated into the specification by reference. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO335 polypeptide is capable of stimulating proliferation of T-lymphocytes.

Appellants recognize that there may be polypeptides that: (i) are structurally related to PRO335 but which do not or, (ii) do not resemble PRO335 in structure but stimulate the immune system through mechanisms unrelated to those of PRO335. These structurally related or unrelated polypeptides, however, would not be encompassed by the instant claims because Appellants claim only those proteins which meet both recitations of the claims, structural and functional. Thus, these recitations clearly act to further define the claimed genus.

The specification further describes methods for the determination of percent identity between two amino acid sequences. (see for example, page 67, line 34 onwards to page 69). The specification also describes methods for the determination of percent identity between two nucleic acid sequences (see for example, page 69, line 25 to page 72, line 8). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 113, line 31, to page 115, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 114). Accordingly, one of skill in the art could identify whether a variant PRO335 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making and modifying the amino acid sequences and methods of preparing the PRO polypeptides (see page 115, line 10, to page 375, line 9).

Therefore, Appellants respectfully submit that the specification provides ample guidance such that one of skill in the art could readily test a variant nucleic acid encoding a polypeptide of PRO335 to determine whether the polypeptide is capable of stimulating proliferation of T-lymphocytes by the methods set forth in Example 74. One of skill in the art would have understood at the time of filing, based on the design of the instant MLR assay (which is designed

to find molecules that increase DC (dendritic cell)-induced T-cell proliferation) and based solely upon the knowledge about DCs and their role in antigen presentation which was widely known that: (i) molecules which enhanced the proliferation of stimulated T-cells would increase the ability of DCs to convert antigens to immunogens, and (ii) such stimulatory molecules would allow antigens that were not usually immunogenic, such as the melanoma or viral antigens described above, to become immunogenic without undue experimentation. Thus, this biological activity together with the well defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, sufficiently defines the claimed genus such that, one skilled in the art, at the effective date of the present application, would have known how to make and use the claimed polypeptide sequences without undue experimentation.

In view of the above, Appellants submit that a valid case for utility has been made and would be considered credible by a person of ordinary skill in the art. Indeed, the logic underlying Appellants' assertion that the PRO335 polypeptides would be useful as an immunostimulant or in providing antibodies for inhibiting immunostimulation is not inconsistent with the general knowledge in the art, and would be considered credible by a person skilled in the art. Accordingly, the claimed nucleic acids encoding PRO335 polypeptides also find utility. Further, Appellants respectfully submit that the Examiner's comments fail to support a *prima facie* case of lack of utility. Accordingly, Appellants believe the rejections of Claims 39-47, 49-52 and 55-58 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, to be improper, and respectfully request withdrawal of these rejections.

ISSUE II: Claim 52 is not Anticipated Under 35 U.S.C. §102(b) by the Amersham Life Sciences Catalog (1996)

Appellant submit that the currently pending claims are not anticipated by the disclosure of pages 348-352 of the Amersham Life Sciences Catalog (1996) because it only discloses **labeled nucleotides** (radioactive and dye-labeled) useful in various assays such as labeling reactions, DNA sequencing, protein kinase assays, etc. These nucleotides clearly do not anticipate the instantly claimed "isolated **nucleic acid molecule consisting of a fragment of the nucleic acid sequence of SEQ ID NO: 289**, or a complement thereof, that **specifically hybridizes** under stringent

conditions." The stringent hybridization conditions are a claimed element of Claim 52 and Appellants submit that the cited nucleotides of the Amersham catalog would not **specifically** hybridize to SEQ ID NO: 289 under the stringent hybridization conditions recited.

Accordingly, Claim 52 is not anticipated by the Amersham Life Sciences Catalog (1996) and hence this rejection should be withdrawn.

CONCLUSION

For the reasons given above, Appellants submit that the MLR assay disclosed in Example 74 of the specification provides at least one patentable utility for the PRO335 polypeptides of Claims 39-47, 49-52 and 55-58. Therefore, Claims 39-47, 49-52 and 55-58 meet the requirements of 35 U.S.C. §112, first paragraph. In addition, the currently pending claims are not anticipated by the disclosure of Amersham Life Sciences Catalog (1996). Accordingly, reversal of all the rejections of Claims 39-47, 49-52 and 55-58 is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-1618 P2C79**).

Respectfully submitted,

Date: March 10, 2006

By: Daphne Reddy
Daphne Reddy (Reg. No. 53,507)

HELLER EHRMAN LLP
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

8. CLAIMS APPENDIX

Claims on Appeal

39. An isolated nucleic acid having at least 80% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290);

(b) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290), lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of (SEQ ID NO: 290);

(d) the nucleic acid sequence of (SEQ ID NO: 289);

(e) the full-length coding sequence of the nucleic acid sequence of (SEQ ID NO: 289); or

(f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,

wherein the polypeptide encoded by said nucleic acid is an immunostimulant.

40. The isolated nucleic acid of Claim 39 having at least 85% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290);

(b) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290), lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of (SEQ ID NO: 290):

(d) the nucleic acid sequence of (SEQ ID NO: 289);

(e) the full-length coding sequence of the nucleic acid sequence of (SEQ ID NO: 289); or

(f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,

wherein the polypeptide encoded by said nucleic acid is an immunostimulant.

41. The isolated nucleic acid of Claim 39 having at least 90% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290);

(b) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290), lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of (SEQ ID NO: 290):

(d) the nucleic acid sequence of (SEQ ID NO: 289);

(e) the full-length coding sequence of the nucleic acid sequence of (SEQ ID NO: 289); or

(f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,

wherein the polypeptide encoded by said nucleic acid is an immunostimulant.

42. The isolated nucleic acid of Claim 39 having at least 95% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290);

(b) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290), lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of (SEQ ID NO: 290):

(d) the nucleic acid sequence of (SEQ ID NO: 289);

(e) the full-length coding sequence of the nucleic acid sequence of (SEQ ID NO: 289); or

(f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,

wherein the polypeptide encoded by said nucleic acid is an immunostimulant.

43. The isolated nucleic acid of Claim 39 having at least 99% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290);

(b) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290), lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of (SEQ ID NO: 290):

(d) the nucleic acid sequence of (SEQ ID NO: 289);

(e) the full-length coding sequence of the nucleic acid sequence of (SEQ ID NO: 289); or

(f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,

wherein the polypeptide encoded by said nucleic acid is an immunostimulant.

44. An isolated nucleic acid comprising:

(a) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290);

(b) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290), lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of (SEQ ID NO: 290);

(d) the nucleic acid sequence of (SEQ ID NO: 289);

(e) the full-length coding sequence of the nucleic acid sequence of (SEQ ID NO: 289); or

(f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927.

45. The isolated nucleic acid of Claim 44 comprising a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290).

46. The isolated nucleic acid of Claim 44 comprising a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290), lacking its associated signal peptide.

47. The isolated nucleic acid of Claim 44 comprising a nucleic acid sequence encoding the extracellular domain of the polypeptide of (SEQ ID NO: 290).

49. The isolated nucleic acid of Claim 44 comprising the nucleic acid sequence of (SEQ ID NO: 289).

50. The isolated nucleic acid of Claim 44 comprising the full-length coding sequence of the nucleic acid sequence of (SEQ ID NO: 289).

51. The isolated nucleic acid of Claim 44 comprising the full-length coding sequence of the cDNA deposited under ATCC accession number 209927.

52. An isolated nucleic acid molecule consisting of a fragment of the nucleic acid sequence of SEQ ID NO: 289, or a complement thereof, that specifically hybridizes under stringent conditions to:

(a) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290):

(b) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO 290), lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of (SEQ ID NO: 290):

(d) the nucleic acid sequence of (SEQ ID NO: 289);

(e) the full-length coding sequence of the nucleic acid sequence of (SEQ ID NO: 289); or

(f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,

wherein said stringent conditions are hybridization in 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate,

5 x Denhardt's solution, sonicated salmon sperm DNA (50 μg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

55. A vector comprising the nucleic acid of Claim 39.

56. The vector of Claim 55, wherein said nucleic acid is operably linked to control sequences recognized by a host cell transformed with the vector.

57. A host cell comprising the vector of Claim 55.

58. The host cell of Claim 57, wherein said cell is a CHO cell, an *E. coli* or a yeast cell.

9. EVIDENCE APPENDIX

1. Declaration of Sherman Fong, Ph.D. under 35 C.F.R §1.132, with attached Exhibits A-E:

A. Current Protocols in Immunology, Vol. 1, Richard Coico, Series Ed., John Wiley & Sons, Inc., 1991, Unit 3.12.

B. Steinman, R.M., "The dendritic cell advantage: New focus for immune-based therapies," *Drug News Perspect.* **13**:581-586 (2000).

C. Gubler, U. *et al.,* "Coexpression of two distinct genes is required to generate secreted bioactive cytotoxic lymphocyte maturation factor," *Proc. Natl. Acad. Sci. USA* **88**:4143-4147 (1991).

D. Peterson, A.C. *et al.,* "Immunization with melan-A peptide-pulsed peripheral blood mononuclear cells plus recombinant human interleukin-12 induces clinical activity and T-cell responses in advanced melanoma," *J. Clin. Oncol.* **21**:2342-2348 (2003).

E. Thurner, B. *et al.,* "Vaccination with Mage-3A1 peptide-pulsed mature, monocyte-derived dendritic cells expands specific cytotoxic T-cells and induces regression of some metastases in advanced stage IV melanoma," *J. Exp. Med.* **190**:1669-1678 (1999).

2. Amersham Life Sciences Catalog, pages 348-352, 1996.

Item 1 was submitted with Appellants' Response filed August 30, 2004, and noted as considered by the Examiner on November 17, 2004.

Item 2 was made of record by the Examiner in the Final Office Action mailed August 11, 2005.

10. RELATED PROCEEDINGS APPENDIX

None - no decision rendered by a Court or the Board in any related proceedings identified above.

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